Parkinson's Disease Research and Education Center & EES
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Mood Disorders in Parkinson's Disease: What's New?

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Acadia Pharmaceutical, Boehringer Ingelheim GmbH, Merck Serono, Ovation

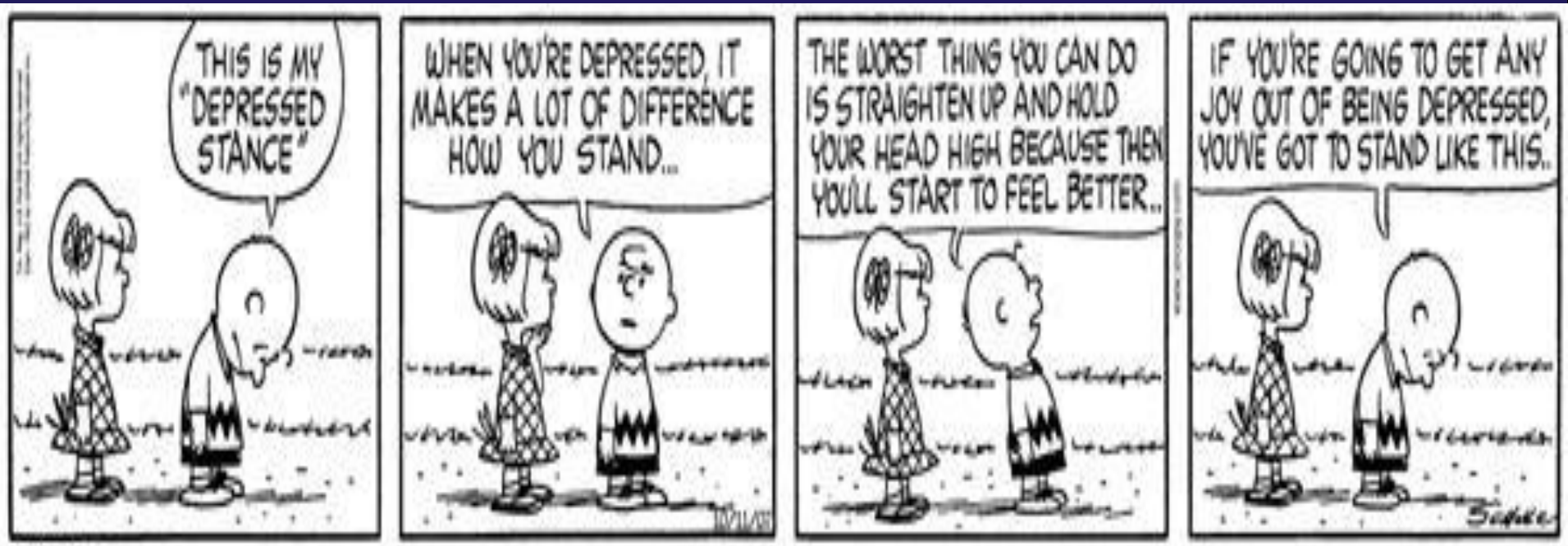
Royalties

Taylor & Francis/Informa

Approved/Unapproved Uses

This presentation may discuss use of medications that do not have FDA approval for treatment of psychiatric aspects of PD

Parkinson's Disease and Depression



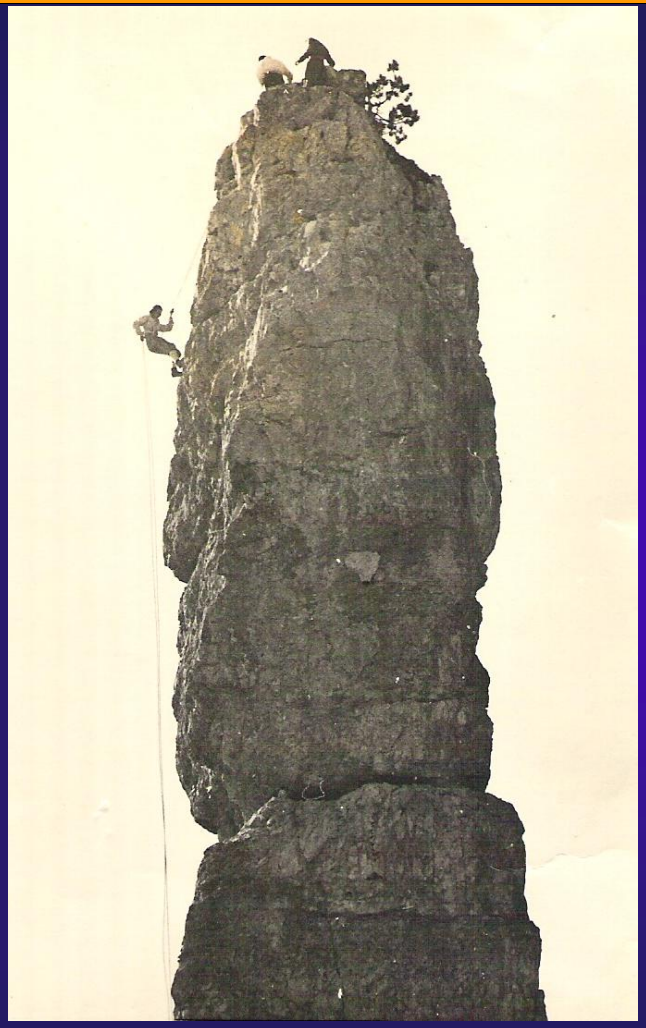
Learning Objectives

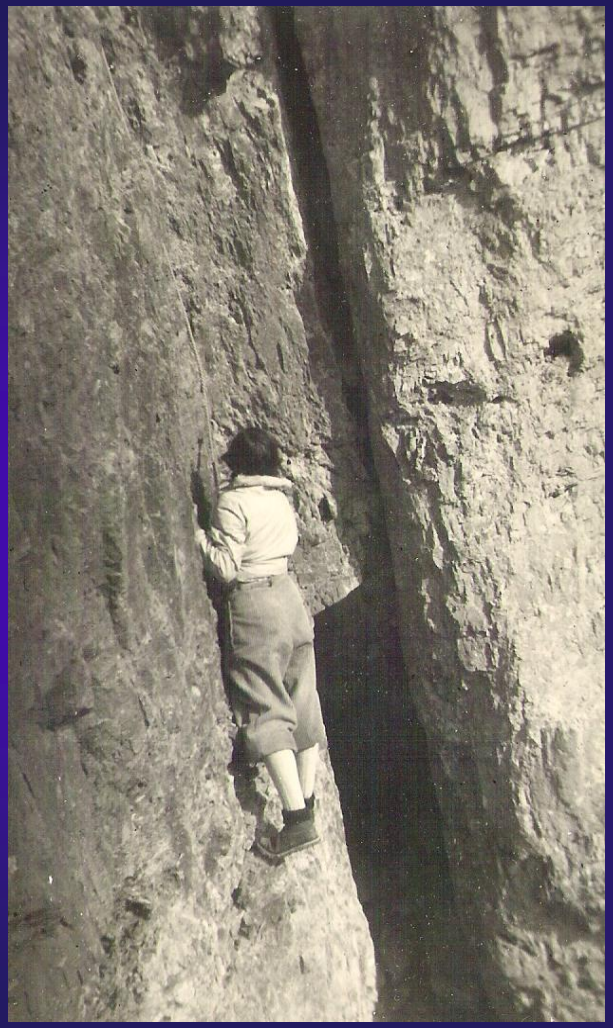
1. Describe the occurrence of depressive phenomena at different stages of PD
2. Recognize the features of depression in PD patients (and PD in depression)
3. Discuss treatment strategies for patients with PD and depression

Case History

- 86 yo WWF, deceased sec NSC met. Lung ca-2009
- Prior National Table Tennis Champ-Senior Division
- Onset Major Depressive Episode age 69
  - Recurrent episodes of depression
- Diagnosed with PD age 72 with dragging foot x 3 years, left hand tremor x 6 months
- Onset Generalized Anxiety Disorder age 80
- Cognitive changes age 80, decline age 82
- Intermittent Visual Hallucinations age 81
- Imbalance age 83

Case History





Outline

I. PD Overview

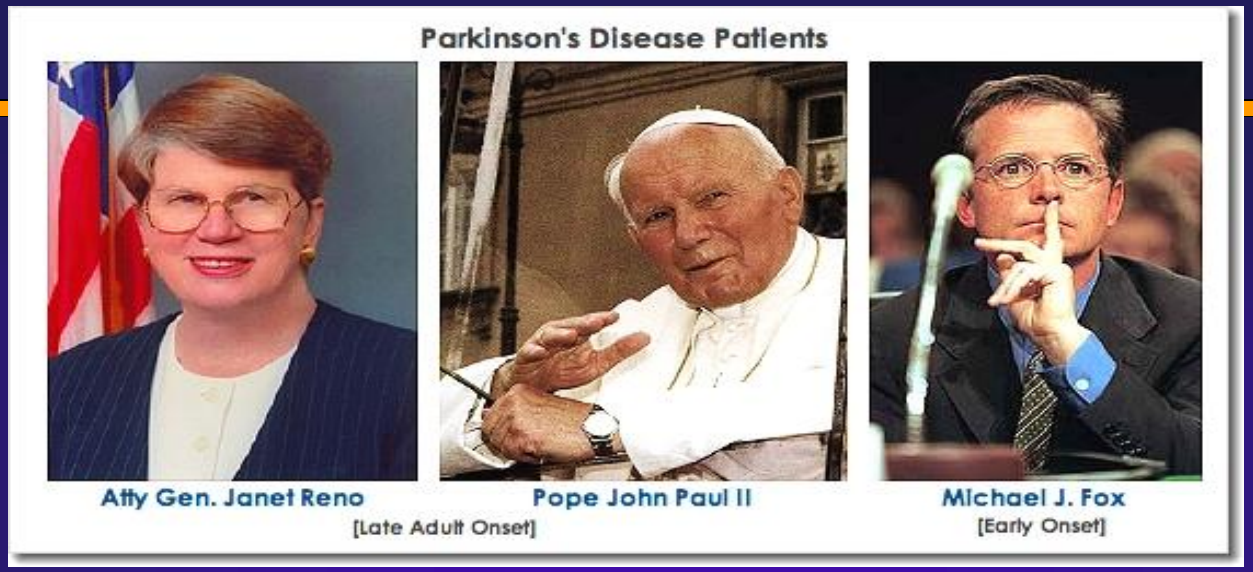
II. Impact of depression on PD Phenotype

III. Recognition of depression in PD

III. Treatment

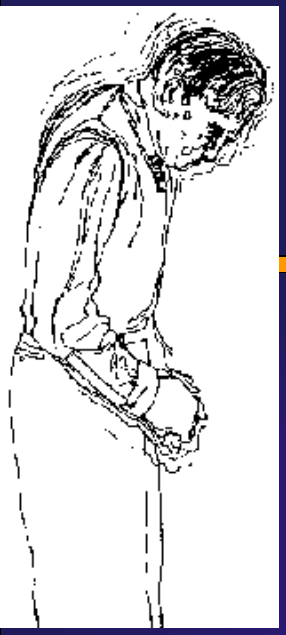
PD Overview

Parkinson's Disease



- Affects ~ 1 million Americans, ~ 0.3% general population
  ~ 1% of the population over age 50
  ~ 2.5% > 70 years; ~ 4% > 80 years
- All races, ethnicities
- Affects Men > Women
- Estimated Direct Costs (2004) $34 Billion/Year

Noyes K et al., Mov Disord 21: 362-372, 2006; Whetten-Goldstein K et al., J Am Ger Soc 45: 844-449, 1997



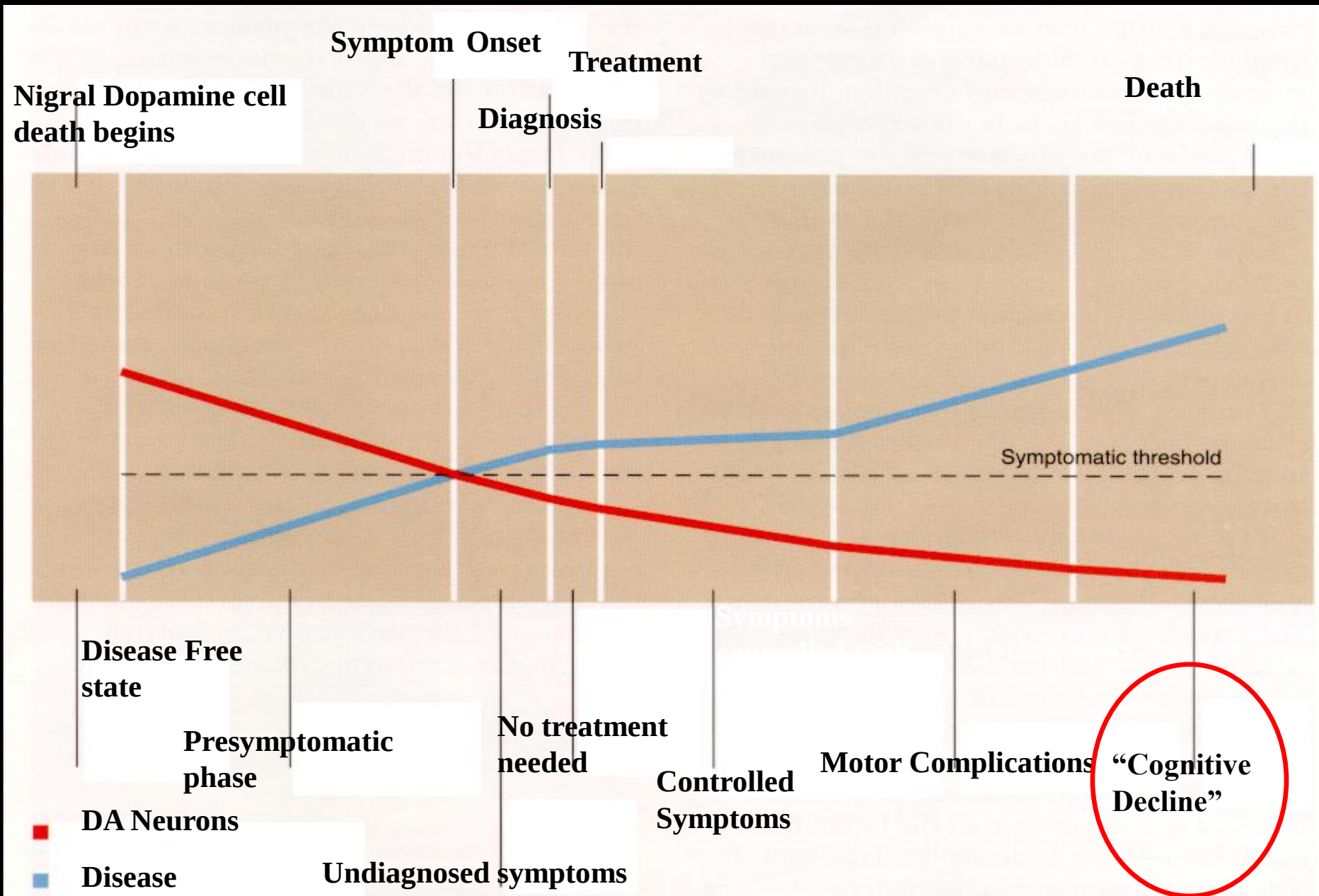
Motor Features of PD

Classic Motor Triad
- Tremor
- Rigidity
- Bradykinesia/Akinesia

- Gait and Postural Disturbances
  - Dragging, Shuffling, Start Hesitation, Festination
  - Later loss of righting reflexes, Unsteadiness, Imbalance
- Absence of Parkinson-Plus Features
- Motor signs ≠ Disability ≠ Psychological distress

Schrag et al., 2001

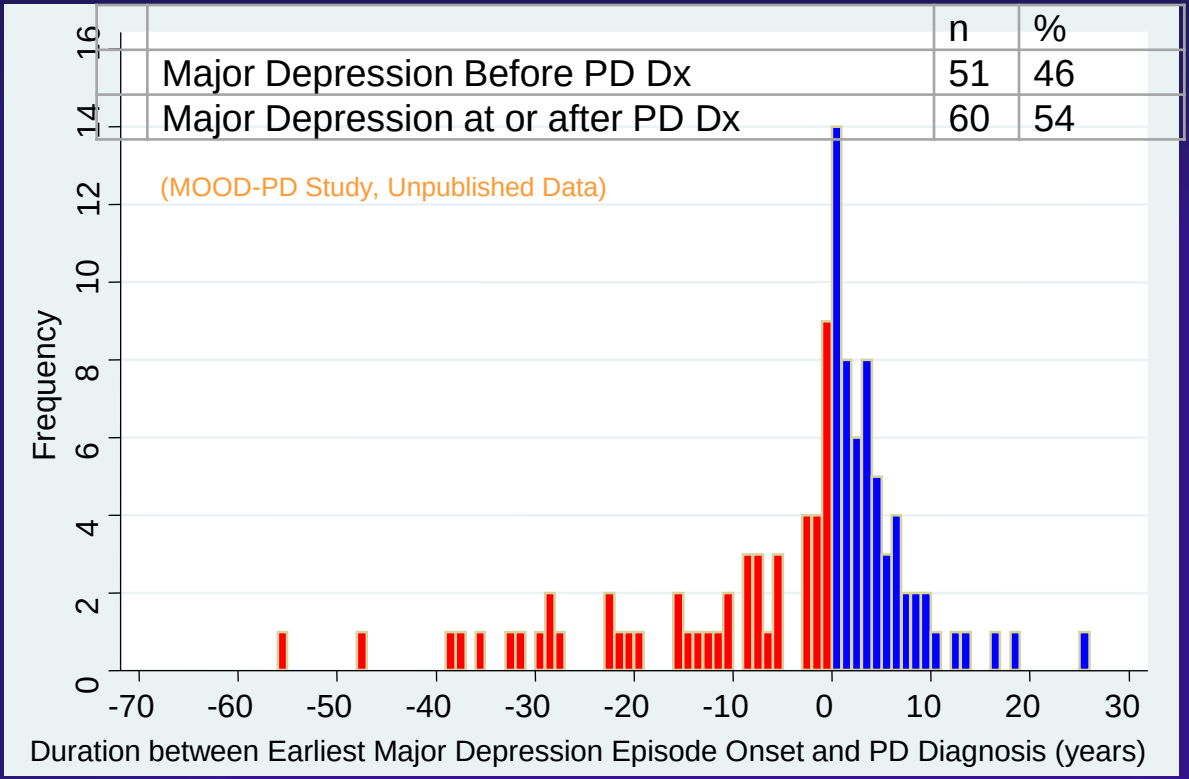
Traditional View of Course of PD



Pre-PD Psychopathology
Risk factor or early symptom of PD?

- **Gonera et al., 1997**
  - 4-8 year prodrome before PD diagnosis - Increased mood and anxiety symptoms
- **Shiba et al., 2000**
  - Up to 20 years before motor signs - anxiety dos (OR=2.2)
  - Up to 5 years before motor signs - depressive dos (OR=1.9)
- **Weisskopf et al., 2002**
  - 12-year follow-up of 35,000 men
  - Relative risk of developing PD (1.5-1.6) - High anxiety and anxiolytic use

Onset of depression is not related to disease stage or disability



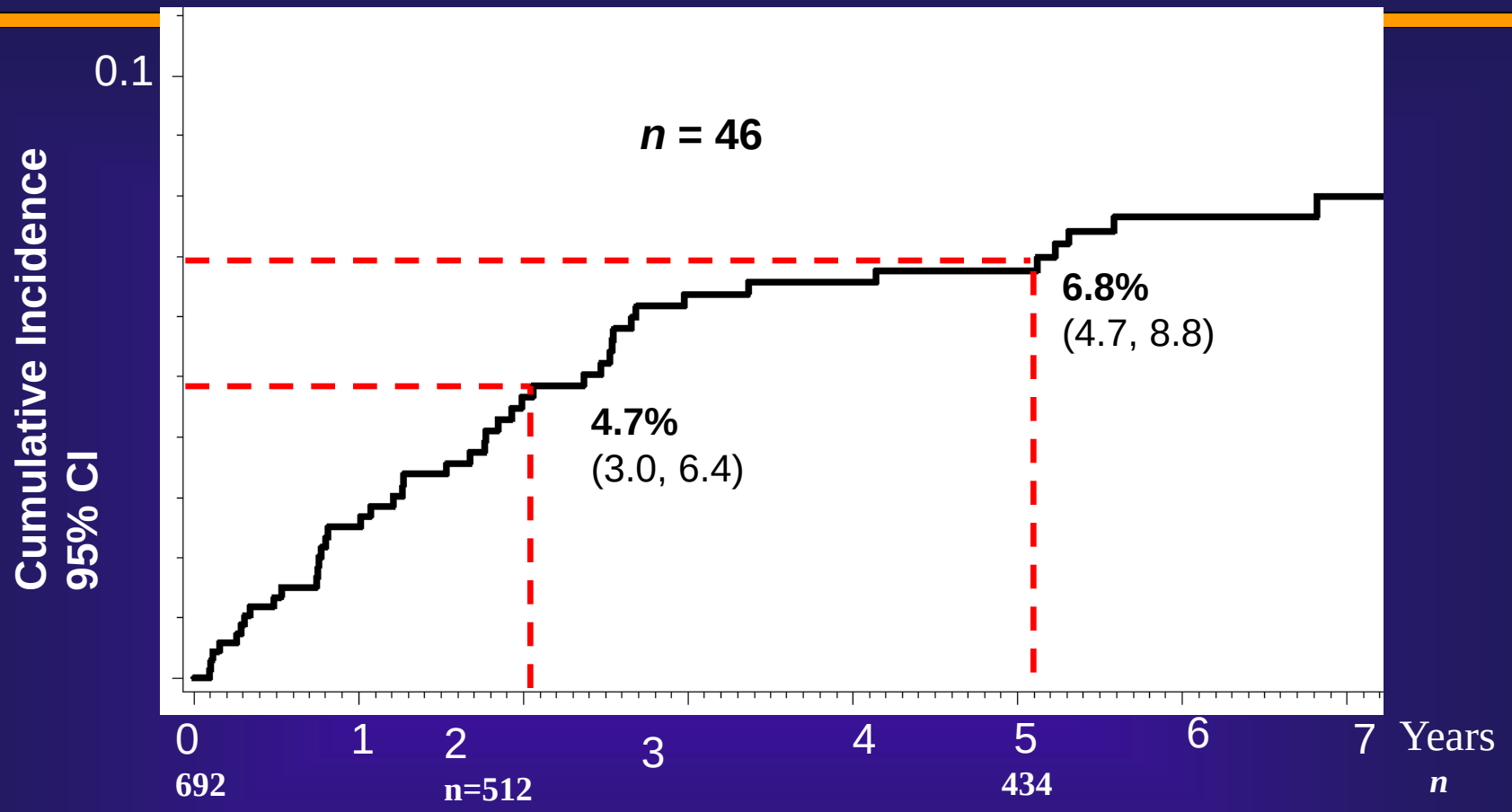
- **Ishihara and Brayne 2006 (review)**
  - On average, affective diagnoses precede PD by 4 to 6 years
  - RR 3.13 (1.95-5.01) Schuurman et al 2002
  - RR 2.4 (1.72-2.93) Nilsson et al 2001
  - RR 2.40 (2.10-2.70) Leentjens et al 2003

Initial Symptoms of PD (n=183)

Symptom	#
Tremor	129 (70%)
Gait disturbance	21
Stiffness	18
Slowness	18
Muscle pain, cramps, aching	15
Loss of dexterity	14
Handwriting disturbance	9
Depression, nervousness	8
Speech disturbance	7
General fatigue, muscle weakness	5
Drooling	3
Loss of arm swing	3
Facial masking	3

Yahr, 1967

Increased rates of Depression in Early PD [DATATOP Study (Uc et al., 2009)]



Annual incidence rate = 1.4% (1.0-1.8)

Time to Depression, based on HAM-D Score = 4.9 2.7 years

Depressive Symptoms Associated With Initiation of Motor Treatment

NET-PD Study/Neuroprotective Treatment Trials

n=413 early untreated PD

- Depressive symptoms - GDS-15≥5
- 27.6% + Depression screen over ~ 15 months
- 40% Depression cases left untreated

- Depressive symptoms predicted
  - Increased ADLS ($p<0.0002$)
  - Increased need for symptomatic PD therapy (HR=1.86; 95% CI 1.29-2.68)

Ravina et al., 2007

Course of Depression

NET-PD Study/Neuroprotective Treatment Trials

- Depressive Symptoms remained mild
- 47% remission within 6 months
- Mild depressive symptoms predicted
  - Development of more severe symptoms (RR=6.16 [95%CI 2.14.17.73])
- Sx severity, older age, longer PD duration predicted failure to remit (HR0.83-0.92)

Ravina et al., 2009

Neuropsychiatric features have greatest impact on quality of life.

Clinical features associated with significantly impaired PDQL (quality of life) scores

	p Value
Depression (BDI>17); n=18	<0.001
MMSE<25; n=13	<0.001
History of hallucinations; n=15	< 0.05
History of falls; n=58	<0.001
Postural instability; n=43	<0.001
Gait impairment; n=61	<0.001
Akinetic-rigid subtype; n=68	< 0.01

Schrag et al, JNNP, 2000

Neuropsychiatric Features – Most disabling over Disease Course

Sydney Multi-center Study – 15-year Follow-up

- n=149, 52 surviving (71 ± 8; 55-86 years)

- Most disabling long term symptoms
  - Cognitive decline - 84%
  - Dementia - 48%, MCI - 36%
  - Hallucinations – 50%
  - Depression – 39%

Hely et al, 2005

Treatment Options in PD

- Levodopa/carbidopa
- Dopamine agonists
  - Bromocriptine
  - Pergolide
  - Pramipexole
  - Ropinirole
  - Rotigotine
- MAO-B inhibitors
  - Rasagiline
  - Selegiline
- Other
  - Anticholinergics
  - Amantadine
  - Benztropine
  - Trihexyphenidyl
- Nonpharmacologic
  - Exercise/PT
  - Acupuncture
  - Deep Brain Stimulation
  - Pallidotomy
  - Other

Antiparkinsonian Medications: Adverse Effects

- Neuropsychiatric
  - Mood Changes
  - Psychosis
  - Confusion/delirium
  - Disinhibition, gambling, hypersexuality

Antiparkinsonian Medications: Fluctuating Effects

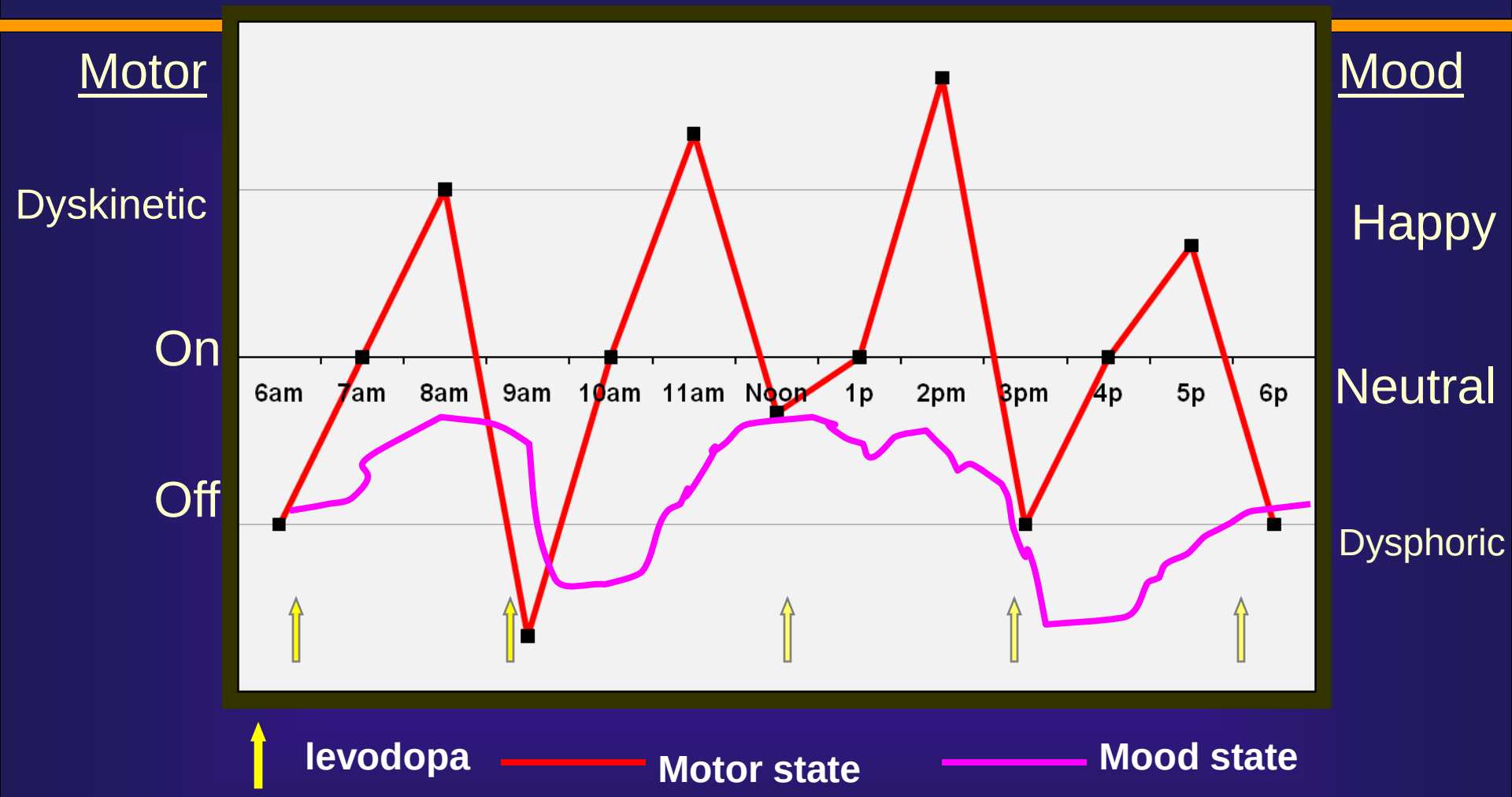
- Motor
  - Loss of efficacy
  - End of dose deterioration/On-off phenomena
  - Dose-limiting side effects
    - Hyperkinesia/Dyskinesias
    - Dystonias
  - Concomitant fluctuating psychiatric & cognitive symptoms

Nonmotor Fluctuations

- **Dysautonomic**
  - Drenching sweats, hot sensation, flushing, dry mouth, dyspnea, dysphagia, constipation, distal cold sensations, excessive salivation, urinary urgency, visual complaints, palpitations, bloating, abdominal pain, chest pain
- **Cognitive/Psychiatric**
  - Slowed thinking, mental hyperactivity, impaired memory, mental emptiness
  - Off-Anxiety (81%), Off-depression (63%), On-hypomania (24%), irritability, psychosis
- **Sensory/Vegetative**
  - Fatigue, akathisia, tightening sensations, tingling, pain

Witjas et al, Neurology 2002; 59: 408-413; Racette et al., J Neuropsychiatry Clin Neurosci 2002; 14: 438-442.

Levodopa-related Fluctuations

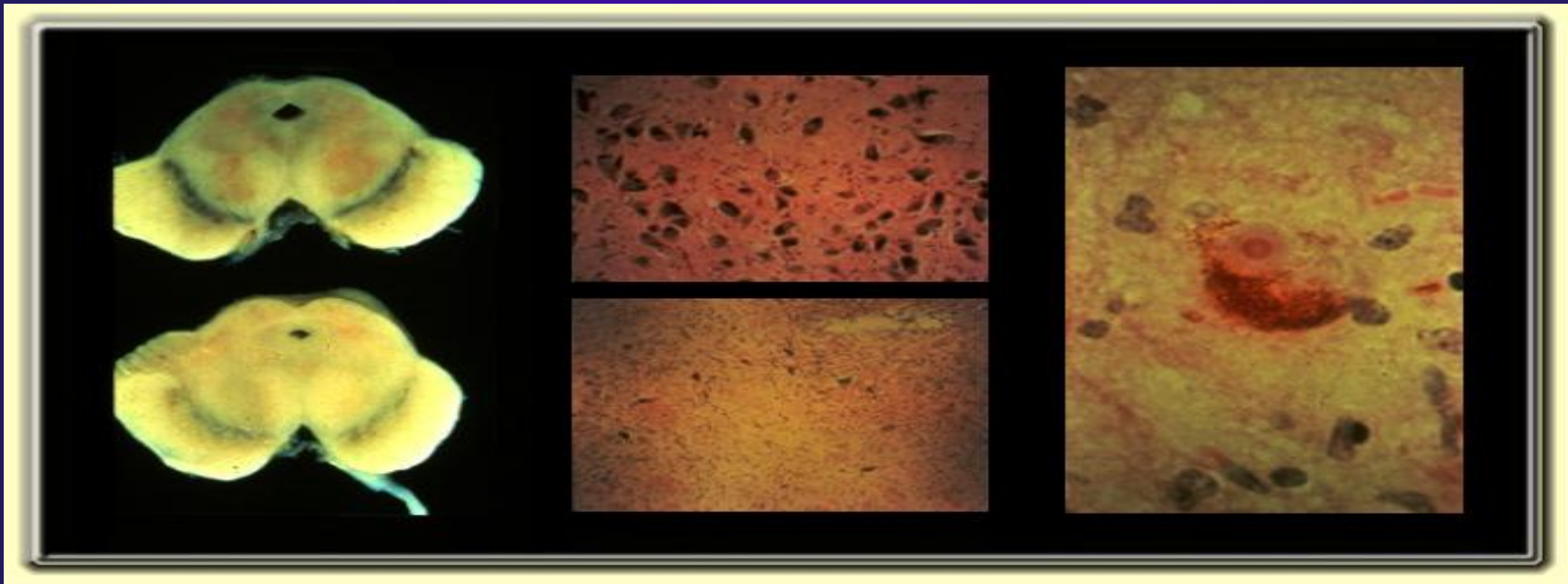


Richard et al, 2004

Neuropathology of Parkinson's Disease

A Dopamine Deficiency Disease

- Substantia Nigra pars compacta Neuronal Loss
- Substantia Nigra Lewy bodies



Neuropathology of PD

Affects multiple dopaminergic systems

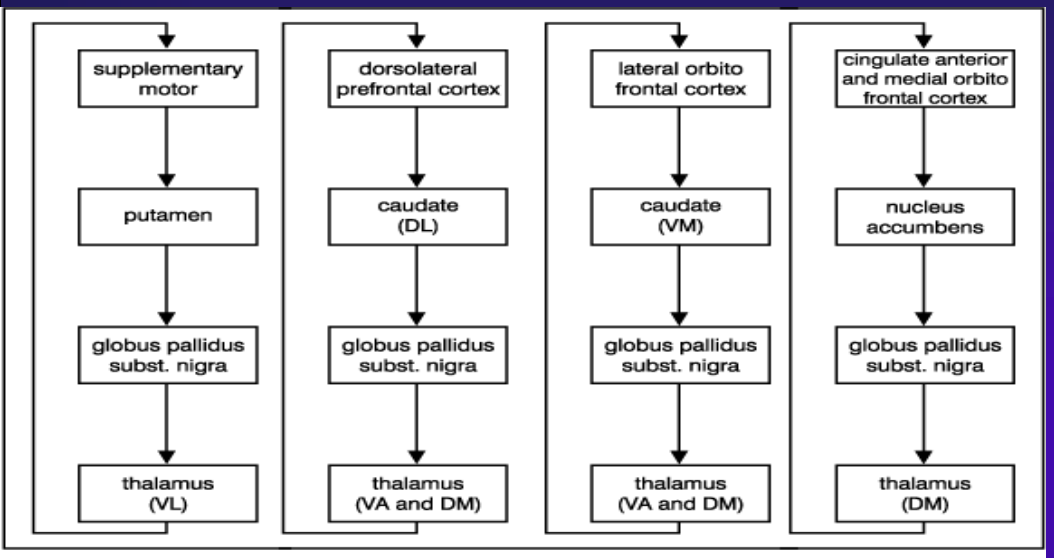
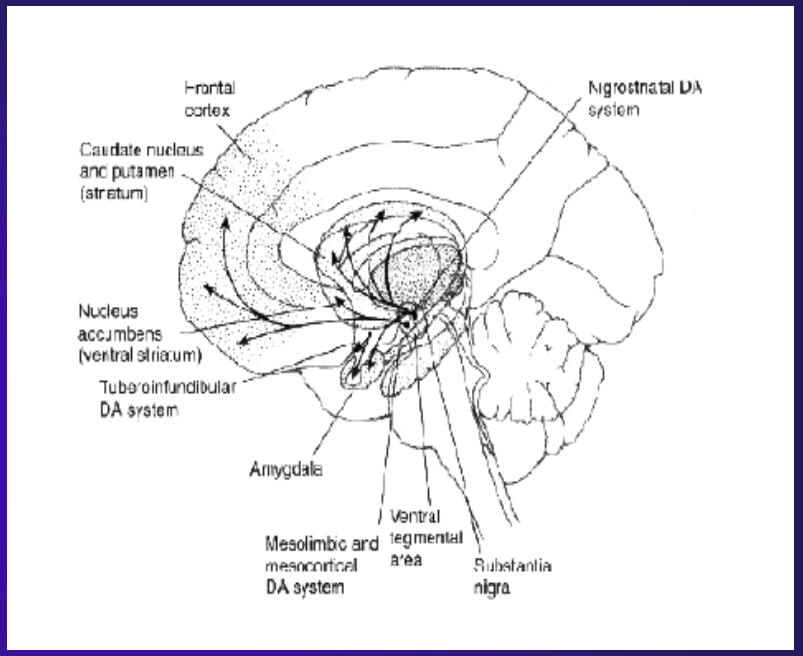


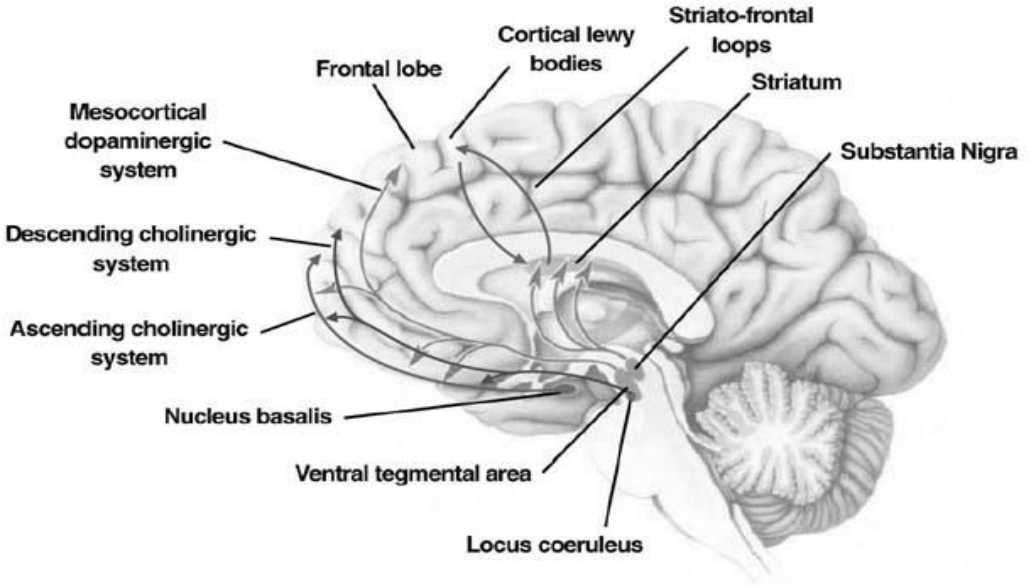
Figure 1 - Frontal-striatal connections.
DL: dorsolateral; DM: dorsomedial; VL: ventrolateral;
VA: ventroanterior; VM: ventromedial.



Cortico-striatal-Thalamic Circuits: Motor, Reinforcement, Higher Order Processing

Mesostriatal, Mesolimbic, Mesocortical Dopaminergic Systems

Non-dopaminergic Neuropathology

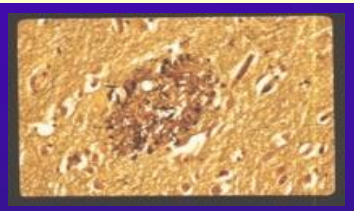


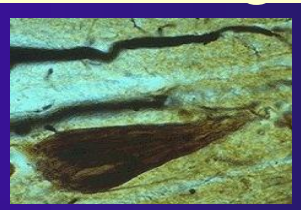
Cognitive changes in Parkinson's disease may result from: 1) degeneration of neural systems (nigrostriatal and mesocortical dopaminergic systems; cholinergic, noradrenergic, serotoninergic systems); 2) cortical lesions (intracytoplasmic Lewy bodies, Alzheimer's like neural changes); and/or 3) their interaction.

Neuronal loss

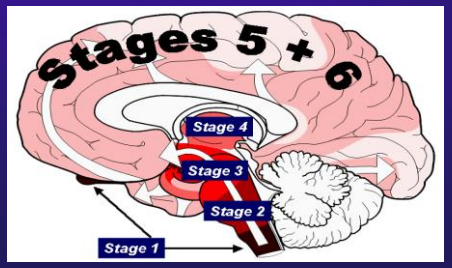
- Locus Coeruleus – NE
- Midbrain raphe – 5HT
- Nucleus basalis – Ach

Alzheimer-type Changes





Lewy Body Pathology



PD Non-Motor Symptom Complex

Neuropsychiatric Symptoms
Mood disturbances
Depression, anxiety, apathy
Psychosis
Hallucinations, delusions
Behavioral changes
Impulsive, repetitive
Cognitive Changes
Selective deficits, Dementia

Sleep Disorders
Restless Legs
Periodic Limb Movements
REM Sleep Behavior Disorder
Non-REM Sleep Mvt Disorders
Insomnia, EDS, Vivid Dreams
Sleep-disordered breathing

Autonomic Symptoms
Bladder DOs-Urgency, Nocturia,
Frequency
Sweating
Orthostasis
Sexual Dysfunction
Dry eyes
GI-drooling, ageusia, dysphagia, reflux,
Constipation, Incontinence

Other symptoms
Sensory – Pain, paresthesias,
Olfactory changes
Fatigue
Seborrhea
Blurred Vision, Diplopia

Chaudhuri KR, Lancet Neurology, 2006

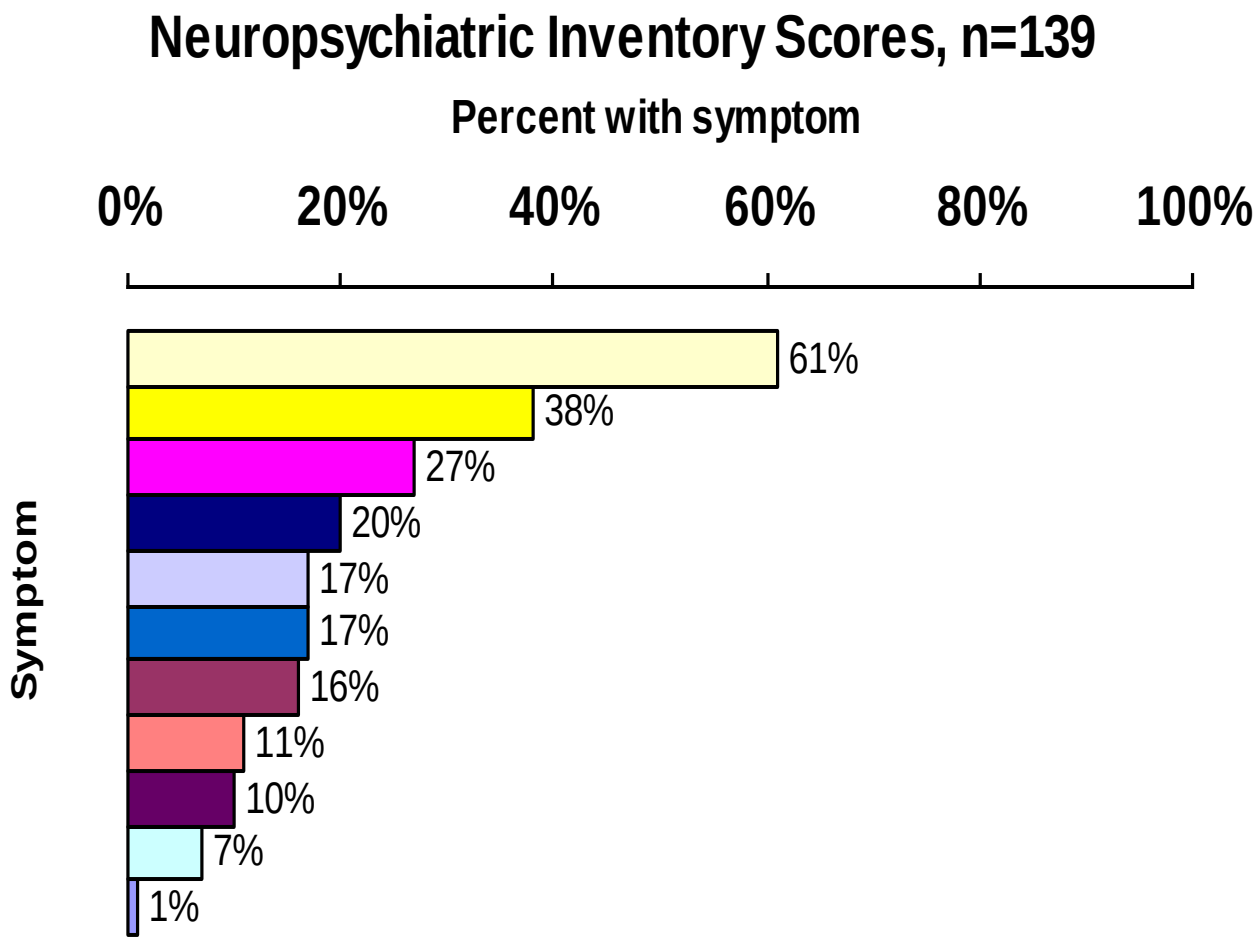
Early Non-motor features correspond to earliest signs of pathology, e.g., Braak's 6-stages

Stage 1 N=21; medulla oblongata	Lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone
Stage 2 N=13; medulla oblongata and pontine tegmentum	Pathology of stage 1 plus lesions in caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus-subcoeruleus complex
Stage 3 N=24; midbrain	Pathology of stage 2 plus midbrain lesions, in particular in the pars compacta of the substantia nigra
Stage 4 N=24; basal prosencephalon and mesocortex	Pathology of stage 3 plus prosencephalic lesions. Cortical involvement is confined to the temporal mesocortex (transentorhinal region) and allocortex (CA2-plexus). The neocortex is unaffected
Stage 5 N=17; neocortex	Pathology of stage 4 plus lesions in high order sensory association areas of the neocortex and prefrontal neocortex
Stage 6 N=11; neocortex	Pathology of stage 5 plus lesions in first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field

Braak H et al, Neurobiology of Aging 24: 197-211, 2003

Prevalence of depressive disturbances in PD

Wide Range of Psychiatric Symptoms

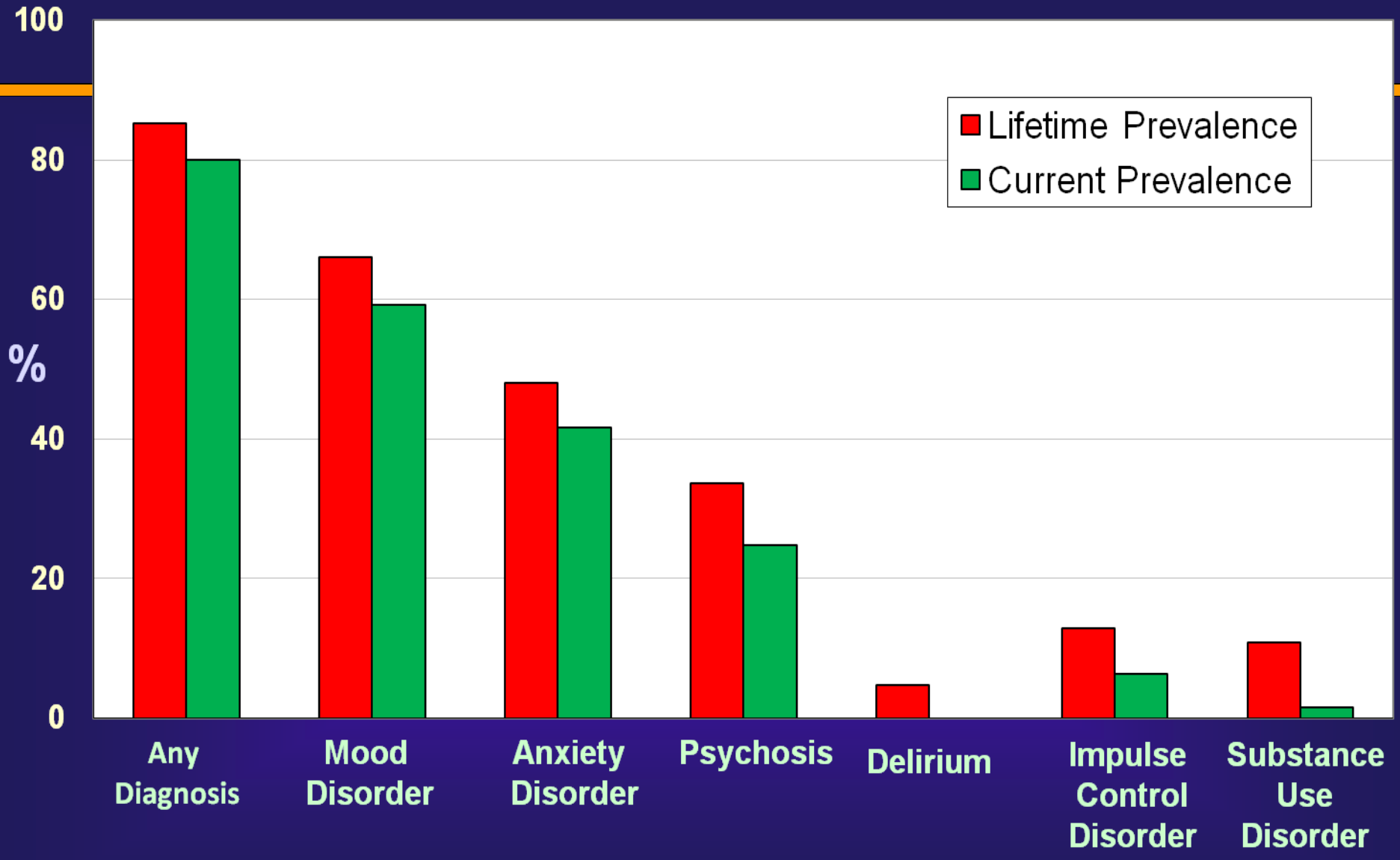


- Euphoria
- Disinhibition
- Irritability
- Aberrant Motor Behavior
- Delusions
- Agitation
- Apathy
- Anxiety
- Hallucinations
- Depression
- Any one symptom

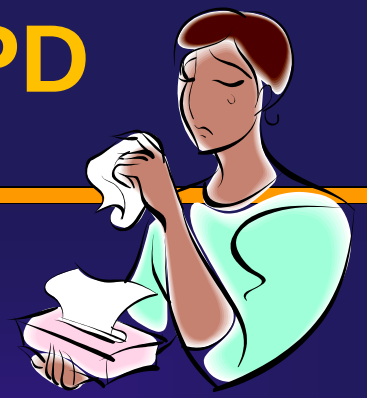
Aarsland et al., 1999, Rogaland, Norway Epidemiological Sample

Range of Psychiatric Diagnoses in PD

(MOOD-PD Study, n=250)



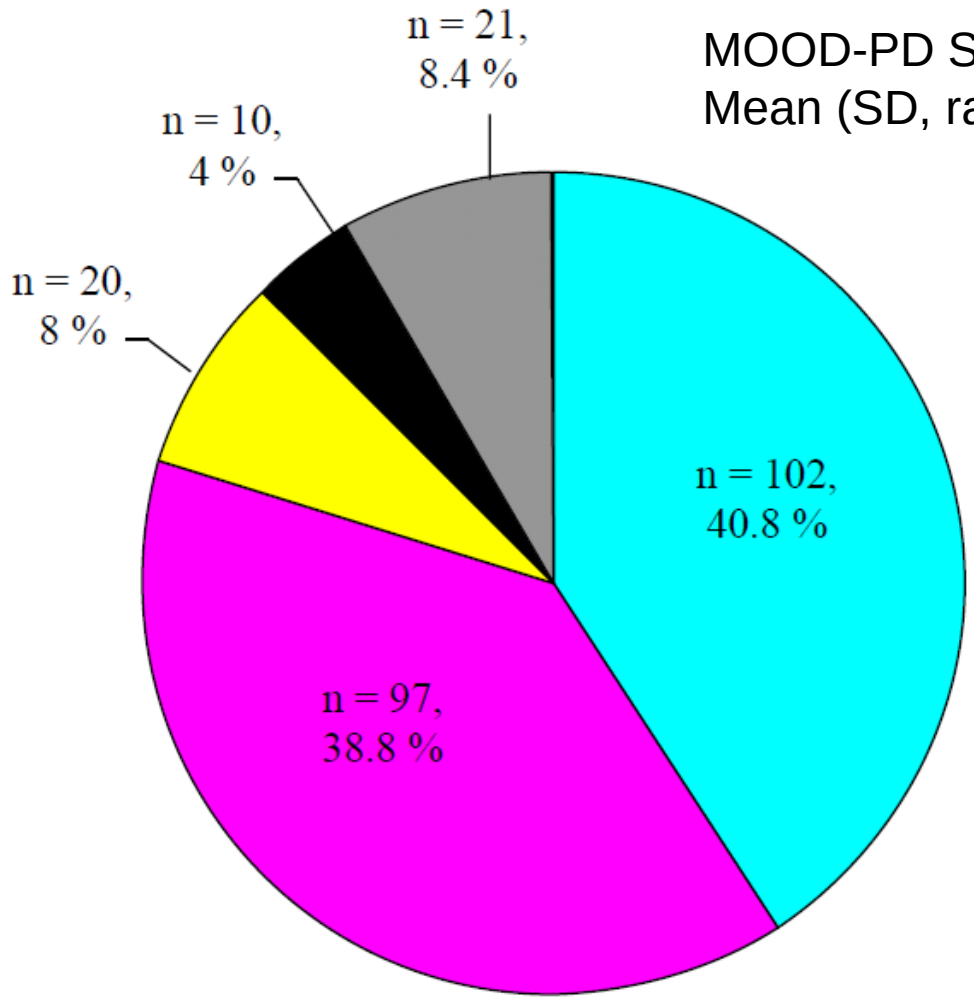
Depressive Disorders in PD



- Epidemiology
  - ~40% prevalence (range 3% - 90%)
  - Clinically significant depressive symptoms 35%
  - Anxiety disorders are a common co-morbidity
  - Rates of recurrence or treatment resistance unclear

Reijnders 2008; Mayeux, 1981; Starkstein, 1992; Meara, 1999; Global PD Survey, 2002; Weintraub 2004

There is a range of depressive diagnoses



MOOD-PD Study (n=250)
Mean (SD, range) PD Duration= 7.8 (6.4, 0-35 years)

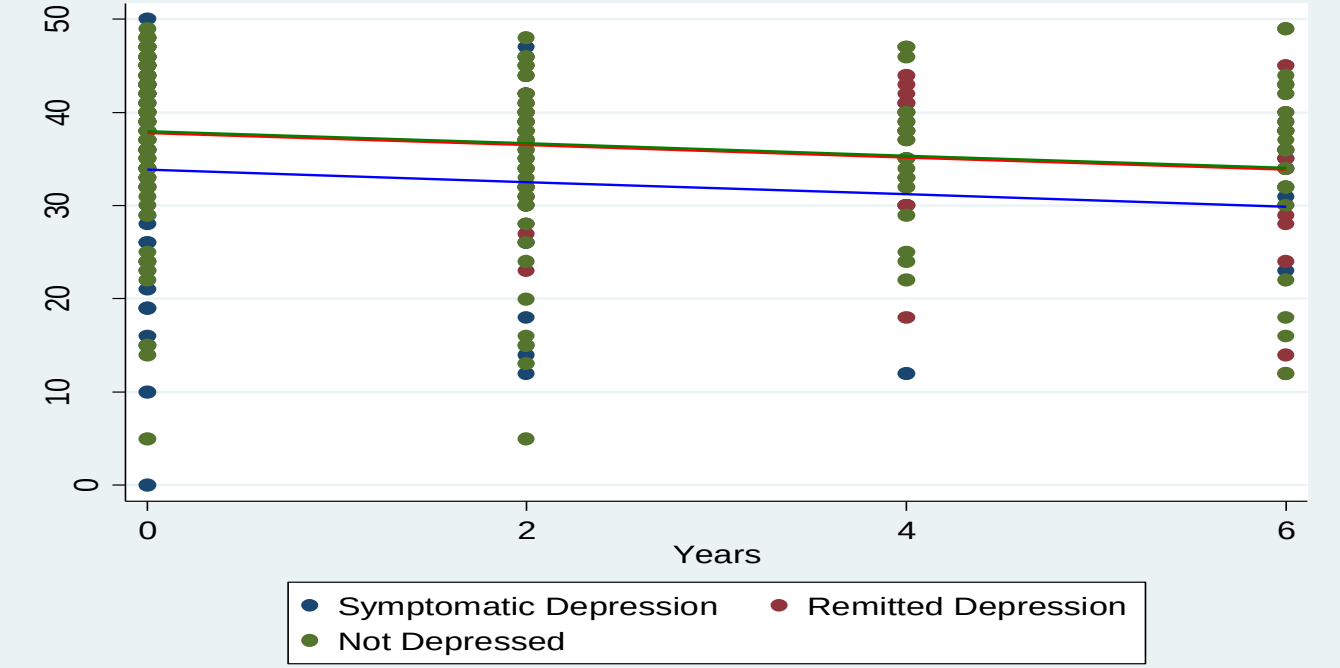
- No Mood Disorder
- Major Depressive Disorder
- Dysthymia or Minor Depressive Disorder
- Bipolar Affective Disorder or Mania
- Other Mood Disorder NOS Only

Palanci 2009

But even worse ...

Symptomatic Depression Worsens Physical ADLs in PD (n=136)

Group differences in Physical ADLs (NWDS) at baseline and 2-year intervals



Marsh et al, 2007

PD Subjects (Baseline)

Age=67.1 (10.5) yrs; PD Duration=9.4 (6.9)yrs
Symptomatic Depression (SD), n=36
Remitted Depression (RD), n=12
Not Depressed (ND), n=88

At any assessment point, subjects with a symptomatic depressive disorder have greater disability, averaging 3.8 points lower on the NWDS score.
(GEE Regression: SD vs ND, B=-3.8, p<.001)

PD Phenotype is Influenced by Depression

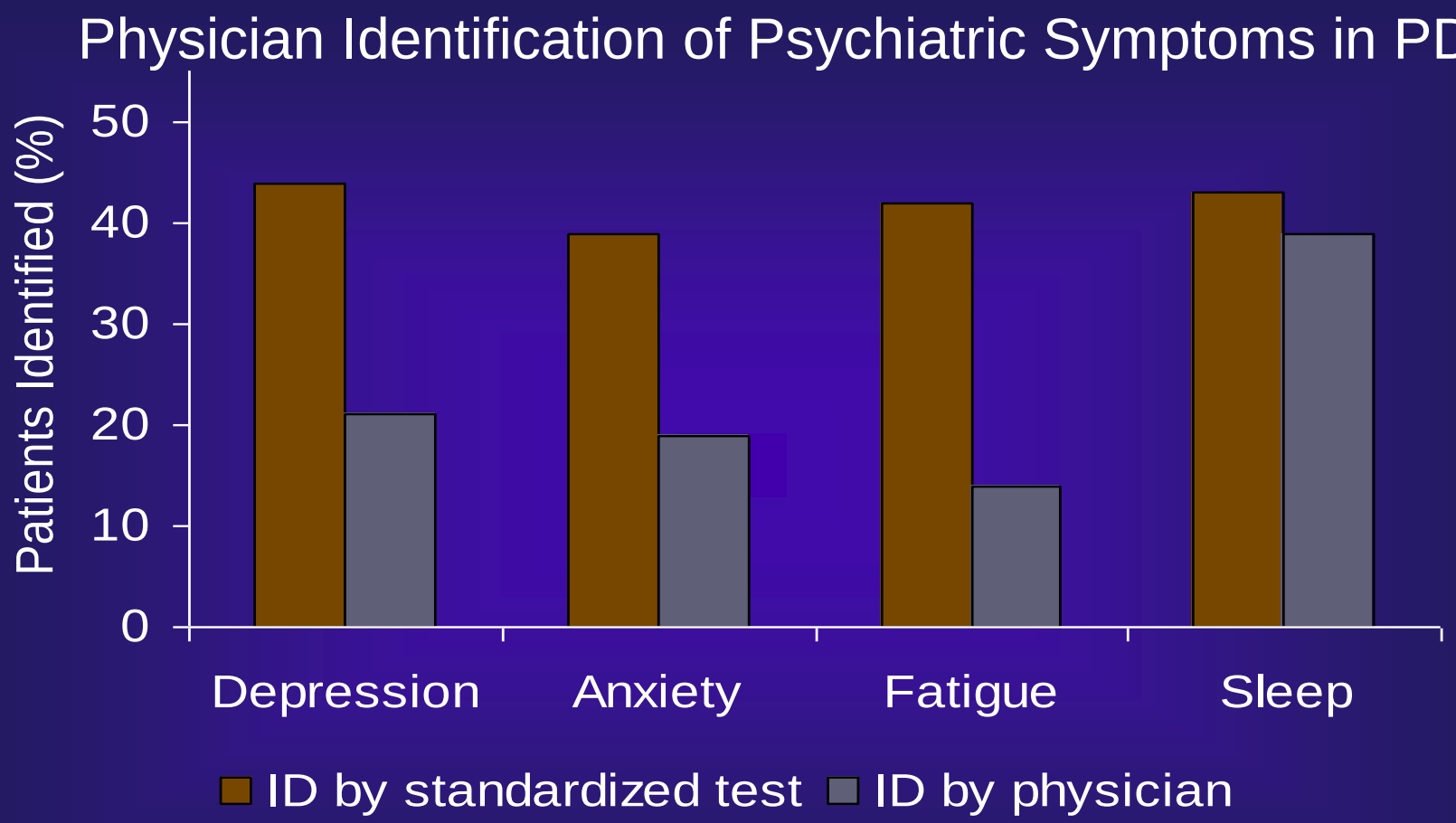
- Associated with increased
  - Motor deficits
  - Cognitive impairment
  - Disability
  - Caregiver burden
  - Economic Strain
  - Concurrent psychiatric conditions

- Depression is not related to disease stage or disability
  - Before motor signs
  - Early or late in PD Course

Reijnders 2008; Mayeux, 1981; Starkstein, 1992; Meara, 1999; Global PD Survey, 2002; Weintraub 2004

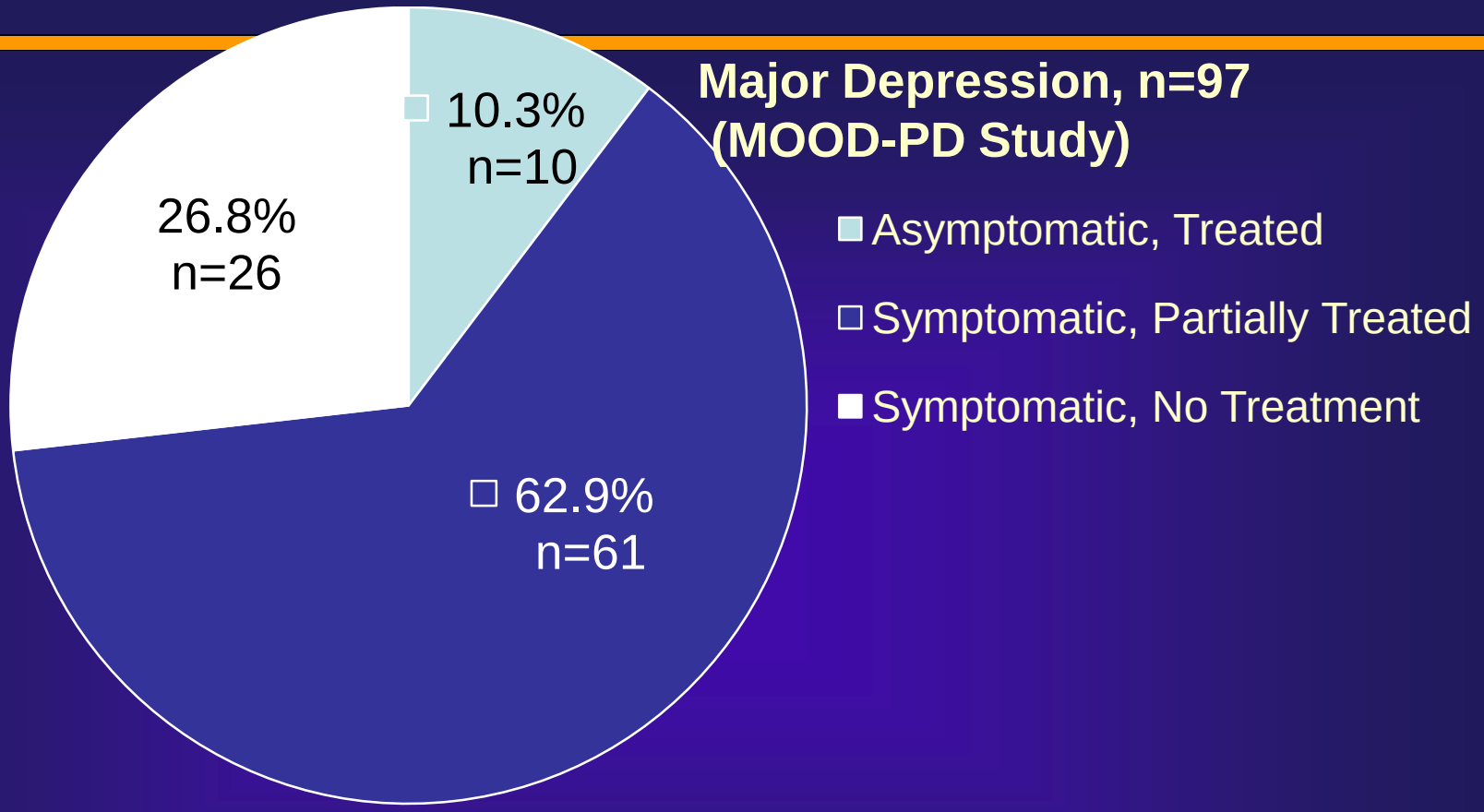
Yet, despite that ...

Under-recognition of Depressive Symptoms



Shulman LM et al. *Parkinsonism Relat Disord*. 2002;8:193-197.

Depressive disorders are unrecognized or undertreated



Duration major depressive episode (n=86) = 182.4 (218.8) weeks
Range 2-1612 weeks. Median 104 weeks.

Palanci *et al.* 2009

Depressive Disorders

- Under-recognized …
  - ~ 75% missed diagnoses (Shulman, 2002)
  - ~ 65% missed diagnoses (Weintraub 2004)
- Under-treated …
  - 94% untreated (Meara 1999)
  - 45% under-treated (Weintraub 2004)
- Mis-treated?
  - Medicare Claims for PD patients (n=10,445)
  - 45.2 % Treated with antidepressant medication (Orsini, 2004)

Recognition of Depression in PD

PD-Depression: Barriers to Recognition

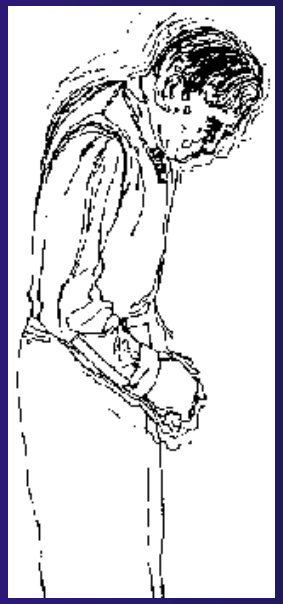
- Motor symptoms
  - Define the disease
  - Primary focus of care/interest
  - Mask psychiatric changes

- Depressive symptoms
  - Regarded as ‘understandable’ reactions
  - Need to be monitored
  - Occur with other mood disorders
  - Stigma
  - Don’t ask, don’t tell

How to Detect Depression in PD

Problem of Overlapping Features

	Major Depression	Parkinson's Disease
Motor	Psychomotor Retardation ± Stooped Posture Restricted/sad affect Agitation	Bradykinesia Stooped Posture Masked Facies Tremor
Cognitive	Impaired Memory Impaired Concentration	
Vegetative	Decreased Energy Fatigue Sleep/Appetite changes	
Somatic	Physical Complaints Sexual, GI, muscle tension	



Depression

≠

Depressive Disorder

Depression

- An emotion characterized by sad and unhappy feelings
- A normal psychological reaction, especially to loss
- A loosely used term
  - Frustration, anger, disgust, anxiety, overwhelmed, apathetic, tired

Depressive Disorder

- A psychiatric (medical) condition
- An abnormal and persistent mental state
- Accompanied by physical and mental changes
- Affects function and causes significant distress

DSM Criteria helpful, but Depressive Disorders have Distinct Emotional Features

- A pervasive change in Mood
  - Persistent sadness
  - Decreased interest and enjoyment, anhedonia
  - Pessimism, hopelessness
  - Negative ruminations
  - Inappropriate guilt
  - Negative view of sense of self
  - Morbid and/or suicidal thoughts
  - Feeling overwhelmed, anxious, unable to cope
  - Irritability

Symptoms of Depressive Disorder Vary

- n=52 PD, Baseline symptoms before treatment for Major Depression (Dobkin 2010)
  - >75% depressed mood, guilt, middle insomnia, early awakening, lack of interest, psychic anxiety, fatigue, low sexual interest
  - <50% suicidal thinking, early insomnia, poor appetite, loss of weight
- n=58 PD, not depressed

Subjective performance of cognition related to mood and not objective performance (Marino 2009)

Depressive Symptom Rating Scales

- **Clinician-rated**

  Hamilton Depression Rating Scale
  Montgomery-Asberg Depression Rating Scale
  Cornell scale for Depression in Dementia

- **Self-rated**
  - Beck Depression Inventory
  - Hospital Anxiety and Depression Scale
  - Geriatric Depression Scale
  - CES-D
  - Zung Depression Rating Scale

Schrag et al. 2008; Williams 2010

*Inclusive Rating Approach Recommended

Methods of Optimal Depression Detection-PD (MOOD-PD) Sample

	Overall Depressive Disorder Prevalence
Depression - Symptomatic	93 (40.6%) 95% CI: 34.2%-47.3%
Major Depression	78 (34.1%) 95% CI: 27.9%-40.6%
Non-Major Depression	15 (6.6%) 95% CI: 2.7%-9.0%
Depression - Remitted	12 (5.2%) 95% CI: 2.7%-9.0%

	No Active Depressive Disorder (n=136)	**Active Depressive Disorder (n=93)**	**p-value**
Age	66.1 (10.0)	66.0 (10.8)	<0.951
Sex	93 M (68%)	60 M 65%)	<0.542
Education	16.5 (3.1)	15.6 (2.6)	<0.025
PD Symptom Duration	8.4 (6.7)	8.7 (6.2)	<0.721
H&Y Stage	I-21 ; I½-7; II-61; II½-27 III-13; IV-5; V-2	I-10; I½-0;II-43;II½-18; III-18; IV-3;V-1	<0.137
UPDRS-Motor	15.9 (9.9) (n=133)	21.6 (12.0) (n=89)	<0.001
MMSE	28.7 (1.3)	27.9 (1.8)	<0.001

Williams iNeurology n press

MOOD-PD Depression Rating Scale Scores

Scale	No Active Depressive Disorder (n=136)	Active Depressive Disorder (n=93)	p-value
BDI-II	6.5 (5.2)	14.7 (7.4)	<0.001
CESD-R	9.3 (10.1)	22.1 (15.1)	<0.001
GDS-30	5.8 (5.2)	13.7 (6.8)	<0.001
IDS-SR	13.3 (8.0)	24.8 (10.1)	<0.001
PHQ-9	3.8 (3.8)	8.9 (5.2)	<0.001
UPDRS-Depression	0.2 (0.5)	1.0 (0.9)	<0.001
HAM-D-17	4.5 (3.2)	11.1 (5.2)	<0.001

Mean (SD)

Williams et al., Neurology n press

Most Depression Scales have Adequate Psychometric Properties in PD Samples

MOOD-PD and Comparison Studies

Measure	AUC	α	Cut-off Score†	Sensitivity	Specificity	PPV	NPV
BDI-II	**0.85**	**0.90**	**≥7**	**0.95**	**0.60**	**0.62**	**0.94**
CESD-R	**0.79**	**0.92**	**≥12**	**0.72**	**0.70**	**0.62**	**0.79**
GDS-30	**0.83**	**0.92**	**≥10**	**0.72**	**0.82**	**0.73**	**0.81**
Ertan 2005	0.89		≥14	0.78	0.85	0.84	0.79
McDonald 2006	0.86		≥10	0.81	0.84	0.58	0.94
IDS-SR	**0.83**	**0.88**	**≥14**	**0.90**	**0.60**	**0.61**	**0.90**
PHQ-9	**0.81**	**0.85**	**≥6**	**0.66**	**0.80**	**0.69**	**0.77**
UPDRS-Depression	**0.75**	**N/A**	**≥1**	**0.70**	**0.77**	**0.68**	**0.79**
Starkstein 2007	0.79	N/A	≥2	0.66	0.81	0.81	0.66
HAM-D-17	**0.86**	**0.77**	**≥7**	**0.77**	**0.76**	**0.69**	**0.83**
‡Leentjens 2000	0.95		≥14	0.88	0.89	0.74	0.96
McDonald 2006	N/A		≥13	0.81	0.82	0.58	0.93
IDS-C	**0.88**	**0.86**	**≥12**	**0.81**	**0.79**	**0.73**	**0.86**
MADRS	**0.88**	**0.83**	**≥8**	**0.74**	**0.88**	**0.81**	**0.83**
‡Leentjens 2000	0.90		≥15	0.88	0.89	0.74	0.96
Silberman 2006	0.84		≥8	0.72	0.82	0.72	0.82

†The cut-off point that maximized the sum of sensitivity and specificity are presented for comparison to other studies, not as a recommendation for a cut-off score to be used in clinical practice.

Williams in press

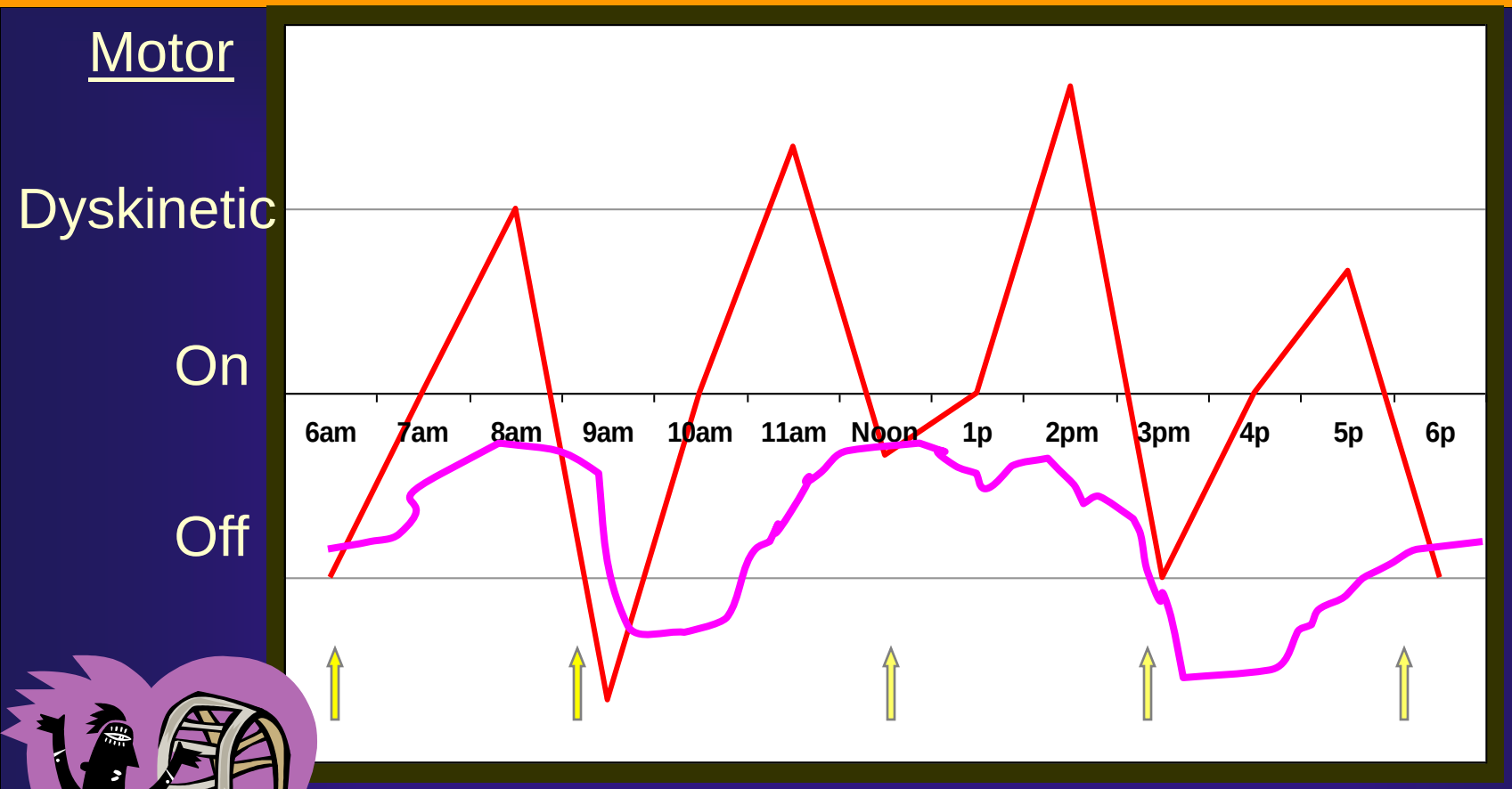
Symptoms Assessed in Different Rating Scales

Instrument	Ham-D	BDI-I	CESDR	PHQ9	GDS
Dysphoria	x	x	x	x	x
Anhedonia	x	x	x	x	x
Weight/Appetite Changes	x	x	x	x	
Sleep Disturbance	x	x	x	x	
Psychomotor Retardation	x		x	x	
Fatigue		x	x	x	x
Worthlessness/Guilt	x	x	x	x	x
Bradyphrenia		?	x	x	x
Suicide/Death	x	x	x	x	
# DSM Criteria	7	7	9	9	5
# Somatic Sx	3	3	4	4	1

DSM Depressive Criteria: Sad mood, Anhedonia/Interest, Appetite, Sleep, Agitation/Retardation, Energy, Self-attitude/guilt, Cognitive, Suicidality

Fluctuating Mood States

Motor and “Non-motor” Fluctuations



levodopa

Motor state

Mood/Cognitive state

Anxiety Disorders

- **Clinical Features**
  - 25-40% prevalence
  - Onset may precede PD
  - Often accompany depressive disorders
  - Not an understandable reaction to motor symptoms
- **Types**
  - Panic Disorder, Generalized Anxiety, Phobias, Wearing-off anxiety/panic

Apathy

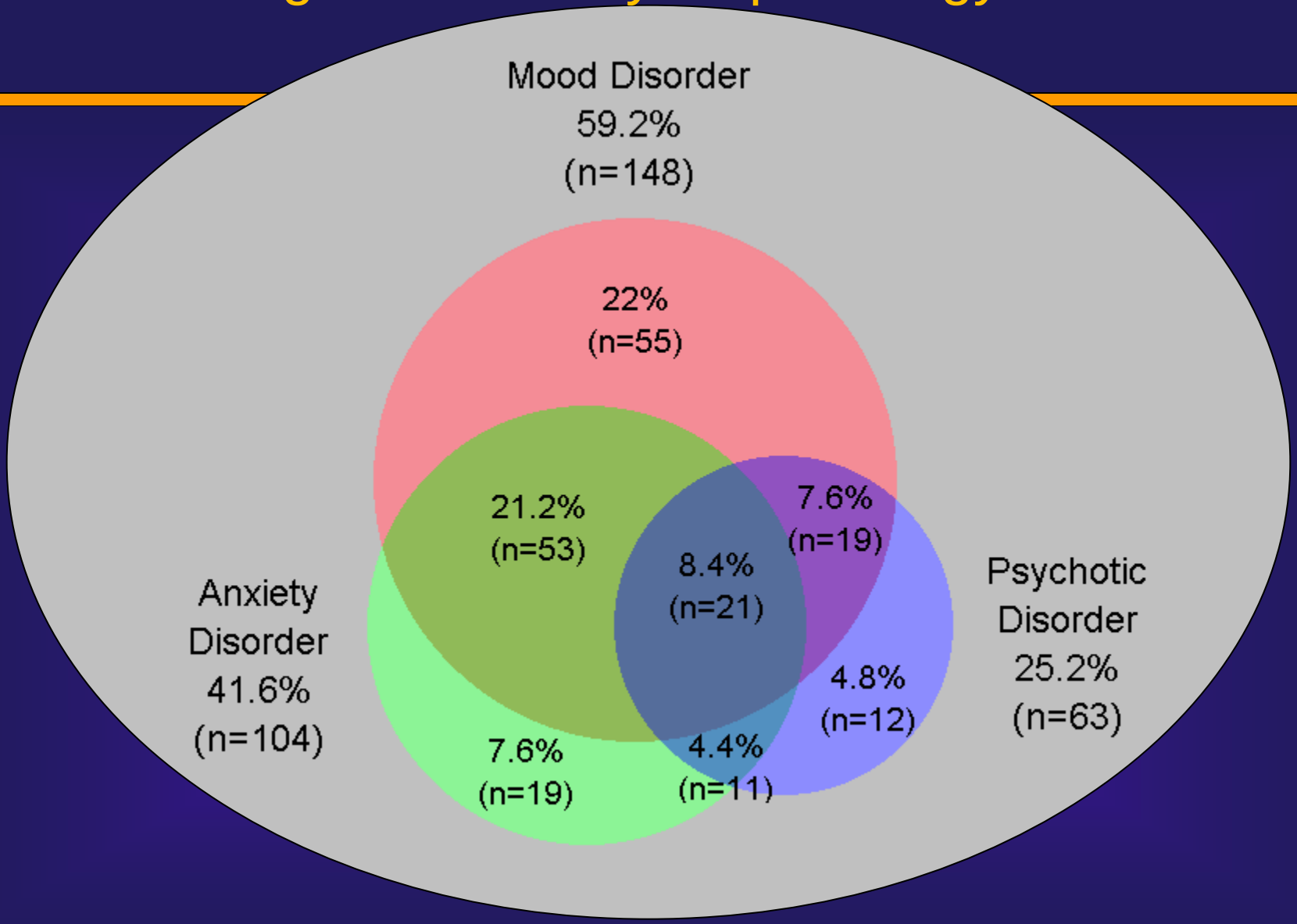
- **Prevalence**
  - ~ 30% as a feature of a depressive disorder
  - ~ 10% as an independent disorder

- **Clinical features**
  - Loss of motivation
  - Emotional indifference
  - Reduced goal-directed activities
  - Patients with primary apathy do NOT complain

Emotionalism/Pathological Crying

- Prevalence
  - 40-50%
  - Associated with Depressive Disorders, Delirium, Benzodiazapines
- Clinical Features
  - Heightened, excessive sentimentality/tear
  - Inappropriate, unmotivated, involuntary
  - Precipitated by a variety of emotions
  - Social embarrassment/Phobic avoidance

Co-morbidities drive complexity in the Assessment and Management of Psychopathology in PD



% of total sample (n=250) with diagnosis

Marsh et al. Unpublished

Treatment of Depression

Psychiatric Treatment

- Targeted and individualized approach
- Adjust/Optimize anti-parkinsonian regimen
- Treat medical conditions/delirium
- Use specific psychiatric medications
  - Anti-depressants
  - Sleep medicines
  - Anti-anxiety medicines
  - Anti-psychotics

• Use Non-pharmacologic Treatments

- Education
  - Psychiatric aspects of PD
  - Coping strategies
  - Caregiver issues
- Psychotherapy
  - Counseling/problem-solving
  - Supportive, directive, insight-oriented, grief counseling, Cognitive-behavioral therapy
  - Caregiver support
- Rehabilitative therapies
  - Occupational, Physical, Speech Therapies
  - Exercise/Exercise classes/Personal trainers
  - Relaxation training
- Social Supports
  - Socialization, Support groups, Home care

Cognitive Behavior Treatment (CBT) Trials for Mood Dos in PD

Armento M, In preparation

	n	Dx	Sessions	Outcome	RCT?
Dobkin 2006	3	MDD	12-14	Min Δ Anxiety	Case Series
Dobkin 2007	15	MDD	10-14	Trend ↓ anxiety	Pilot study
Dobkin in press		MDD	10-14	↓ Depression	Yes
Dreisig 1999	79	Depression	6	Impr Anx	1 month
Feeney 2005	4	Depr/Anxiety	8 group	No Δ Anxiety	Pilot
Macht 2007	3	Depr, Social anxiety, freezing	12-18 months	↓ anxiety	Case series
Veazey 2009	14	Anxiety/Depression	9 (8 on phone)	↓ anxiety (BAI)	Yes-CBT vs Support grp

Components of Various CBT Trials in PD Patients

- Basic CBT components: Automatic thoughts, Triggers, PD specific adaptations
- Problem Solving
- Breathing strategies
- Exposure
- Activity Scheduling
- Stress management
- Behavior Modification
- Sleep Hygiene
- Relaxation
- Cognitive Restructuring
- Caregiver Strategies to reinforce therapy for patient
- Self Monitoring
- Health Promotion
- Symptom (depression/anxiety) management
- Social Skills Training
- Written strategies

Armento M, In review

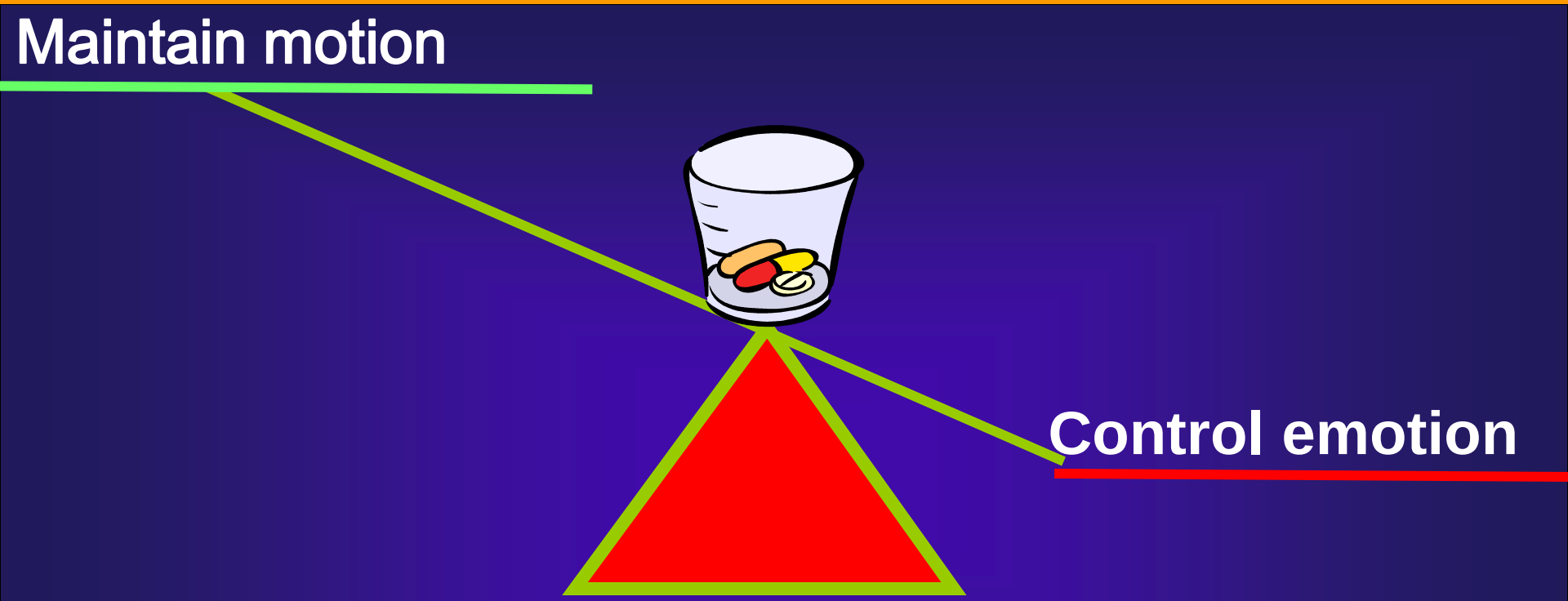
Coping Strategies

- Best if
  - Flexible
    - Vary Active versus Passive Approaches
  - Dynamic
  - Individualized

Frazier and Marsh, 2005

Pharmacological Treatments

The Motion–Emotion Conundrum



Cummings JL. *N Engl J Med.* 1999;340:801-803.

Antidepressants

Class	Reuptake Inhibition
SNRIs	Serotonin-Norepinephrine Tricyclic Antidepressants, Venlafaxine, Duloxetine
NDRIs	Norepinephrine-Dopamine Buproprion
SSRIs	Serotonin Fluoxetine, sertraline, paroxetine, fluvoxamine, es/citalopram
SARIs	Serotonin Antagonist Trazodone, nefazodone
NASAs	Norepinephrine/ Serotonin Antagonists Mirtazipine
ECT	

Antidepressant studies

- **Paroxetine (Paxil)**
  - Chung et al., 2005, n=12
    - No effects on PD symptoms
    - May affect balance
- **Nefazodone (Serzone) vs Fluoxetine (Prozac)**
  - Avila et al. 2003, n=16
  - Both reduced depressive symptoms
  - Motor symptoms improved on Nefaz0done
- **Citalopram (Celexa)**
  - Menza et al., 2004, n=10, open-label
    - Celexa improved depressive and anxiety symptoms
  - Wermuth et al., 1998: No difference between placebo and Cit
- **Amitryptiline vs fluoxetine**
  - Serrano-Duenas, 2002: Ami>Fluoxetine, but +++Side-effects
- **Sertraline vs placebo**
  - Leentjens et al., 2003, n=12: No group difference

Antidepressant studies

- **Atomoxetine (**Weintraub et al., 2010)
  - Norepinephrine Reuptake inhibitor
  - n=55 PD patients, 8week RCT
  - Depression unchanged
  - Improvement global cognition (MMSE score)/enhanced attention

- **Citalopram** (Menza et al., 2004)
  - SSRI
  - n=10, 8week Open-label Trial
  - Improved depression and anxiety
  - Imrprovement global cognition (MMSE score)/enhanced attention

- **Citalopram** (Culang et al 2009)
  - N=174 unipolar depression, >75 years, no PD
  - 8-week trial RCT
  - Non-responders: Decline in verbal fluency, psychomotor speed
  - Responders: improved visuospatial functioning (not c/t placebo)
  - Seek additional treatment for non-response

Antidepressant studies

- **Dopamine agonists**
  - Moller et al., 2005; Reichman et al. 2004
    - Open-label pramipexole ↓ PD Depressive symptoms
  - Barone et al. 2006, n=67
    - 12 wk RCT pramipexole (1.5-4.5 mg/d) vs sertraline (50 mg/day)
    - More pts in remission on pramipexole (61% vs 27%)
  - Barone et al. 2010, n=287
    - 12 wk RCT pramipexole (0.125-1 mg tid) vs Placebo
    - Decreased Depressive and Motor Symptoms on pramipexole
    - Improved depression independent of motor function

Antidepressant studies

- **Recent placebo-controlled trials**
  - Devos et al 2008, n=48
    - 14 days: Desipramine 75 mg > Citalopram 20 mg, Placebo
    - 30 days: Desipramine = Citalopram > Placebo
  - Menza et al 2009, n=52
    - 8 weeks: Nortriptyline (64 mg) >paroxetine 32 mg, placebo
  - Richard et al (in press) (SAD-PD Study), n=115, 17 sites
    - 12 weeks: Paroxetine (24 mg), venlafaxine XR (121mg)> Placebo
    - Remitters (Ham-D$\leq$7 at week 12): PAR=44%, VEN=37%, PLB=32%
    - Responders (Ham-D $\geq$ 50% $\downarrow$ baseline to Week 12
      - PAR=68%, VEN 53%, PLB 44%

Antidepressants are Effective for PD-Depression, but Response often Incomplete

- **N=52, Major Depression/Dysthymia + PD**
  - 8 week trial: Nortriptyline vs paroxetine vs placebo
  - Clinical response: 50% reduction in Ham-D score
    - Nortriptyline superior to placebo and paroxetine
    - 16 responders (3 paroxetine, 4 Placebo, 9 NTP)
    - 36 nonresponders (15 paroxetine, 13 placebo, 8 NTP)
  - Responders
    - Sig improved Mood, middle insomnia, interest, somatic anxiety
  - Residual symptoms in Responders
    - >50% depressed mood, lack of interest, psychic anxiety, low energy

Menza et al., Neurology 2009; Dobkin et al., AGJP 2010

Important Side Effects/Interactions

- Potential for hypertensive Crisis or Serotonin Syndrome
  - Selegeline, Rasagaline plus MAO's
- Orthostasis
- GI Upset
- Sedation
- Anticholinergic side effects
- Benzodiazepine side effects
- Increased parkinsonism
  - Antidepressants (+)
  - Lithium
  - Sodium Valproate
  - Amoxapine
  - Neuroleptics

Conclusions

- Depressive Disorders
  - Common in PD over its course
  - Have a negative impact
  - Are under-recognized
  - Have features that overlap with motor symptoms of PD as well as other psychiatric conditions
  - Are treatable
- Treating depressive disorders effectively, and to remission, reduces excess disability